Lung Cancer (2008) **60**, 366—373

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Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath

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Received 25 July 2007; received in revised form 15 October 2007; accepted 23 October 2007

KEYWORDS
Endobronchial ultrasonography;
Navigational bronchoscopy;
Peripheral pulmonary lesion;
Thin bronchoscope;
Transbronchial biopsy;
Virtual bronchoscopy;
Virtual bronchoscopic navigation

Summary We developed a bronchoscope insertion guidance system that produces virtual images by extracting the bronchi by automatic threshold adjustment, and searching for the bronchial route to the determined target. We used this system in combination with a thin bronchoscope and endobronchial ultrasonography with a guide sheath (EBUS-GS), and evaluated its practicability, usefulness and safety.

The subjects were 31 patients with 32 peripheral pulmonary lesions. Computed tomography (CT) data were transferred into this system, and virtual bronchial images were automatically produced by setting the lesion as the target. While virtual images with the target were displayed for comparison with real images by the system, a thin bronchoscope was advanced to the target bronchus. Transbronchial biopsy (TBB) was then performed by EBUS-GS.

The system automatically produced virtual images to a median of fifth- (third- to seventh-) order bronchi. In all patients, the thin bronchoscope could be guided along the planned route, and observation to a median of fifth- (third- to seventh-) order bronchi was possible. Thirty lesions (93.8%) were successfully visualized by EBUS, and 27 (84.4%) could be pathologically diagnosed. In lesions $\leq$30 mm in size, the EBUS visualization yield was 91.7% (22/24), and the diagnostic yield was 79.2% (19/24). The median total examination time was 22.3 (9.8—41.5) min.

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doi:10.1016/j.lungcan.2007.10.022

In summary, using the bronchoscope insertion guidance system, virtual images can be readily produced, and the bronchoscope can be successfully guided to the target. This method is promising as a routine examination method in the biopsy of peripheral pulmonary lesions.

1. Introduction

Due to recent advances in computed tomography (CT) apparatuses and an increasing spread in their use, especially in the introduction of low-dose helical CT in lung cancer screening [1], peripheral pulmonary lesions are being detected with greater frequency. As a diagnostic method for these lesions, X-ray fluoroscopy-guided bronchoscopy is commonly used because it causes few complications. However, the reported diagnostic yield for small peripheral pulmonary lesions by transbronchial biopsy (TBB) ranges widely from 20 to 84% [2—10]. The diagnostic yield is lower for smaller and more peripheral lesions. One of the reasons for this result is that small lesions cannot be confirmed by X-ray fluoroscopy alone, and it cannot be confirmed whether biopsy forceps or a brush accurately hit the lesion. To overcome this problem, CT fluoroscopy [11,12], endobronchial ultrasonography (EBUS) [13,14], and the electromagnetic method [15,16] have been used to confirm lesions diagnosed by TBB. EBUS is advantageous over the other methods because of the absence of X-ray exposure and because there is no need for expensive equipment other than an ultrasonography system. EBUS with a guide sheath (EBUS-GS), which allows repeated accurate biopsy of a lesion using an ultrasound probe with a guide sheath, was recently developed [17] and good results have been obtained [18].

At present, bronchoscopic examination for small peripheral pulmonary lesions is performed after evaluating the bronchial route to the nodular shadow based on chest images such as CT images. However, it is often time-consuming to identify the bronchi leading to the lesion during bronchoscopy based only on axial CT images. This not only increases the patient's burden but also prevents the diagnosis of small peripheral pulmonary lesions. To overcome this problem, we have proposed virtual bronchoscopic navigation (VBN), in which VB images of the path leading to a peripheral lesion are used to assist in navigation for the insertion of a bronchoscope [19,20]. Good results have been reported for VBN used in combination with CT-guided ultrathin bronchoscopy [21,22] or EBUS-GS [23]. However, VBN is problematic as a potential method of supporting physicians who perform bronchoscopy. In actual bronchoscopy, unlike in VB, the bronchoscope tip can be moved only up or down, and the bronchoscope should therefore be appropriately rotated at the time of its insertion; however, virtual images previously produced shift from real bronchoscopic images [24]. To solve this problem, we developed a navigation system that displays virtual images indicating the target in comparison with real images [25]. This novel navigation system makes the accurate navigation of the bronchoscope to the target bronchus possible. Another problem with VBN is that virtual image production depends on software performance and the experience of the physician who produces the images. Thus, in the peripheral area, if the threshold is inappropriate, bronchial branching may be overlooked or inaccurate branching images may be produced. As a result, the bronchoscope may be guided to the wrong bronchus [24]. A certain level of experience is therefore essential to produce accurate virtual images.

In the present study, we developed a bronchoscope insertion guidance system, consisting of a VBN system with additional functions, specifically, the extraction of the bronchi by automatic adjustment of the threshold when the target is set, and a search function to identify the bronchial route to the target for virtual image production. This system was used in combination with a thin bronchoscope and EBUS-GS for the bronchoscopic diagnosis of peripheral pulmonary lesions, and its practicability, usefulness and safety were evaluated.

2. Materials and methods

2.1. Study subjects

The subjects were 31 patients with a total of 32 peripheral pulmonary lesions treated at Gifu Prefectural General Medical Center between May 2005 and April 2006. Peripheral pulmonary lesions were defined as lesions surrounded by pulmonary parenchyma and not visible on bronchoscopy. The procedures used in the study were in accordance with the Helsinki Declaration of 1975. The institutional review board for human research approved the study protocol. All patients were provided with a detailed description of the examination and were informed that this was a new approach. Informed consent was obtained from all patients.

2.2. Virtual image production by the bronchoscope insertion guidance system

First, CT examination was performed using a multidetector CT scanner (Aquilion; Toshiba, Tokyo, Japan) with the following parameters: 120 kV, 0.5 mm collimation, 16 detectors, pitch of 15, and rotation time of 0.5 s. All lung fields were scanned during a single breath-holding period. The digital imaging and communications in medicine (DICOM) data of CT were transferred into the bronchoscopic insertion guidance system (prototype; Olympus Co., Ltd., Tokyo, Japan), and the starting point was set at the trachea. Based on axial, coronal and sagittal images, the lesion was set as the target. The target is expressed as a sphere whose radius can be changed (Fig. 1). Once the target was set, the airway was extracted according to an automatically set threshold, and the bronchial route to the target was displayed on each cross-sectional image (Fig. 2). Bronchography showing the route can also be displayed 3-dimensionally (Fig. 3). When the mark on the displayed route is moved from the starting point to the target, corresponding cross-sectional images are displayed. When multiple

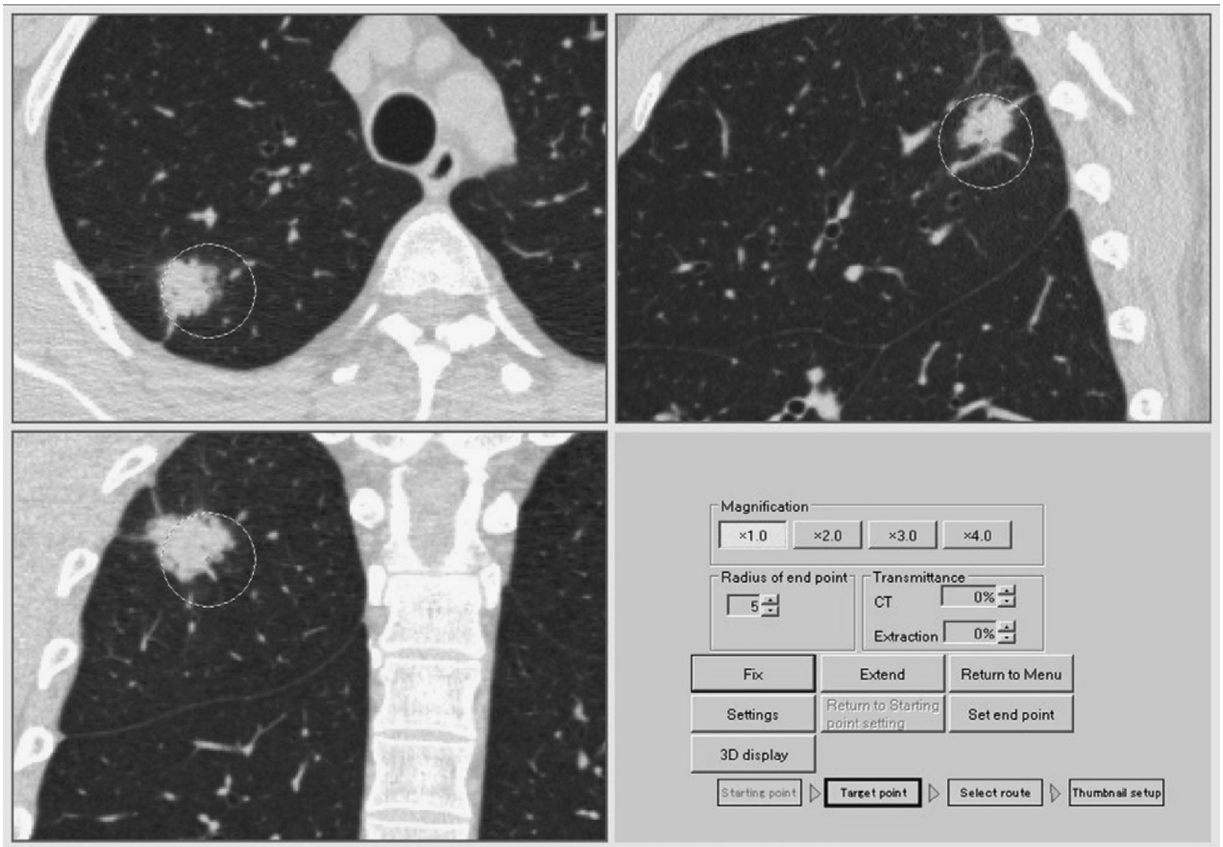

Fig. 1 Target setting. The target (white circle) is set, centering on the involved bronchus in the lesion based on axial, coronal and sagittal images. A small nodular shadow was observed in the right S2.

routes are displayed, the route that allows easier insertion of the bronchoscope can be selected based on the cross-sectional images. When the route has been selected, virtual images along it are automatically produced and displayed as animations. While the virtual images are advanced to show the route of the bronchoscope, the bronchus to which the bronchoscope should be inserted at each branching site is marked and registered as a thumbnail (Fig. 4). The time required for each procedure in the present study was recorded.

2.3. Navigation of a thin bronchoscope with the system

Bronchoscopy was performed using a thin bronchoscope (BF-type P260F; Olympus: external diameter, 4.0 mm; channel diameter, 2.0 mm) in a room equipped with radiographic fluoroscopy apparatuses. Each patient was premedicated with 25 mg hydroxyzine and, when necessary, with 0.5 mg atropine sulfate. Local anesthesia of the upper respiratory tract was performed with 2% lidocaine. After insertion of a thin bronchoscope into the trachea, the use of the system was initiated. As we previously reported [25], the thin bronchoscope was advanced to the target bronchus as far as possible under direct vision while virtual images were displayed for comparison with real images (Figs. 5 and 6). The time required for the use of the system to navigate the thin bronchoscope was recorded.

2.4. EBUS-GS

Subsequently, EBUS-GS was performed using an endoscopic ultrasound system (EU-M30S; Olympus) equipped with a 20 MHz mechanical radial-type probe (XUM-S20-17R; Olympus: external diameter, 1.4 mm) and a guide sheath (prototype; Olympus: external diameter, 1.9 mm). The guide sheath-covered EBUS probe was inserted through the bronchoscope working channel and advanced to the peripheral pulmonary lesion to obtain an EBUS image. After localizing the lesion using EBUS imaging, the probe was removed, leaving the guide sheath in the peripheral lesion. Biopsy forceps (prototype; Olympus) and a bronchial brush (BC-203D-2006; Olympus) were introduced via the guide sheath to provide specimens for pathological and cytological examination. When the lesion could not be visualized by EBUS, we considered that the probe did not reach the lesion and discontinued the examination immediately. X-ray fluoroscopy was performed mainly in repeated biopsy when it was necessary to confirm the absence of the displacement of the guide sheath and the adequate opening of the forceps.

3. Results

Our subjects consisted of 31 patients (22 males, nine females; median age, 72 (42—80) years) with 32 lesions. The median lesion size was 21 (10—53.5) mm: $\leq$2 cm, 15 lesions;

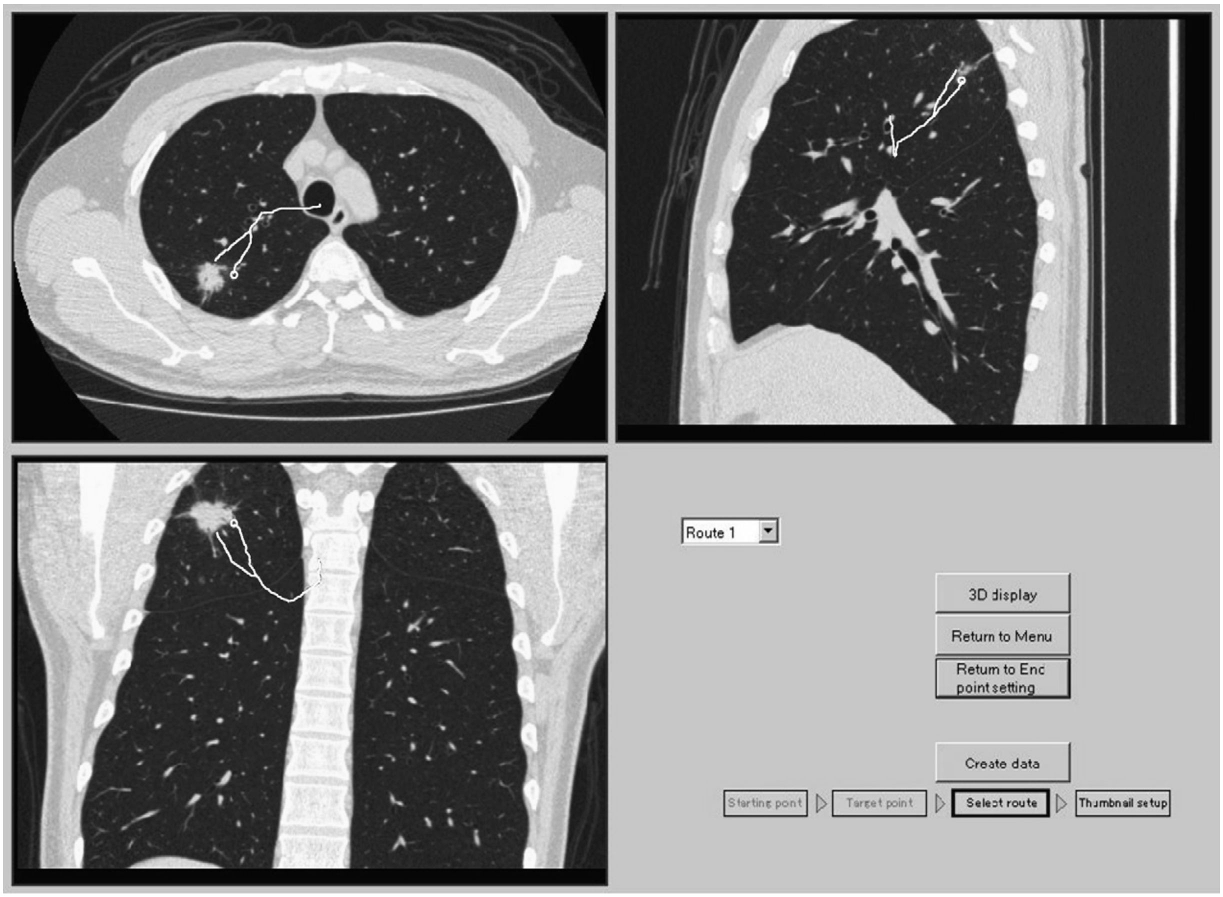

Fig. 2 Bronchial route to the target (2D display). The routes to the target (white lines) are displayed after an automatic search on each cross-sectional image. In this case, two routes were displayed by automatic search.

and >3 cm, eight lesions. Eleven lesions were located in the right superior lobe, seven in the right inferior lobe, 10 in the left superior lobe, and four in the left inferior lobe. Twelve lesions could not be observed by X-ray fluoroscopy.

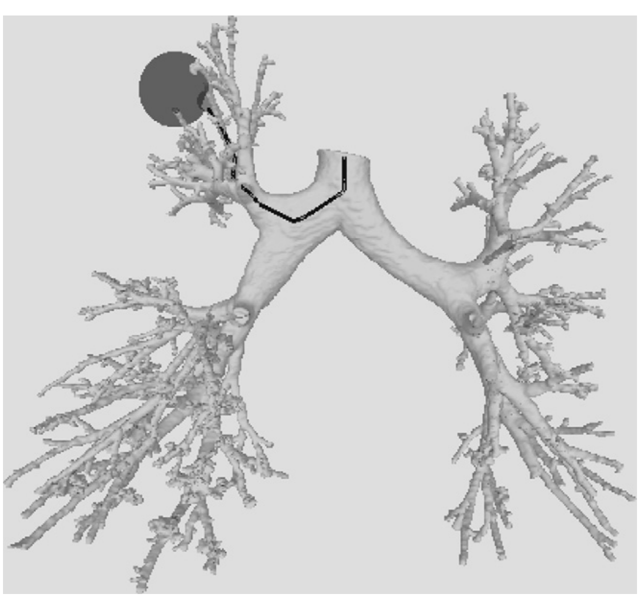

Fig. 3 Bronchography. The relationship between the target (sphere) and route (line) is 3-dimensionally displayed.

Using the present system, virtual images to a median of fifth- (third- to seventh-) order bronchi were successfully produced. The median time required for virtual image production was 14.4 (9.5—19.3) min. The median manual operation time was 6.5 (4.4—9.9) min, and the median automatic system operation time was 7.4 (4.3—11.8) min.

The thin bronchoscope allowed observation to a median of fifth- (third- to seventh-) order bronchi. In all cases, bronchial branching on virtual images was consistent with that on real images, and the guide sheath-covered EBUS probe could be inserted to the target bronchus under direct vision. The navigation time of the thin bronchoscope using this system was 1.6 (0.9—4.8) min.

Of the 32 lesions, 30 (93.8%) were successfully visualized by EBUS. Of the two lesions that could not be visualized, one showed no involved bronchus, and the other was a ground-glass opacity (GGO) lesion. These lesions were finally diagnosed by operation as lung cancer (adenocarcinoma). The 30 lesions visualized by EBUS were subsequently biopsied. The median number of obtained tissue samples was five (4—8). Diagnosis was possible in 27 lesions (84.4% of all lesions): 22 cases of lung cancer (adenocarcinoma, 15 lesions; squamous cell carcinoma, two; small cell carcinoma, two; and histological type unknown, three), one of malignant lymphoma, two of pneumonia, one of pulmonary tuberculosis, and one of pneumoconiosis. In the other three lesions, adequate tissue could not be obtained by biopsy,

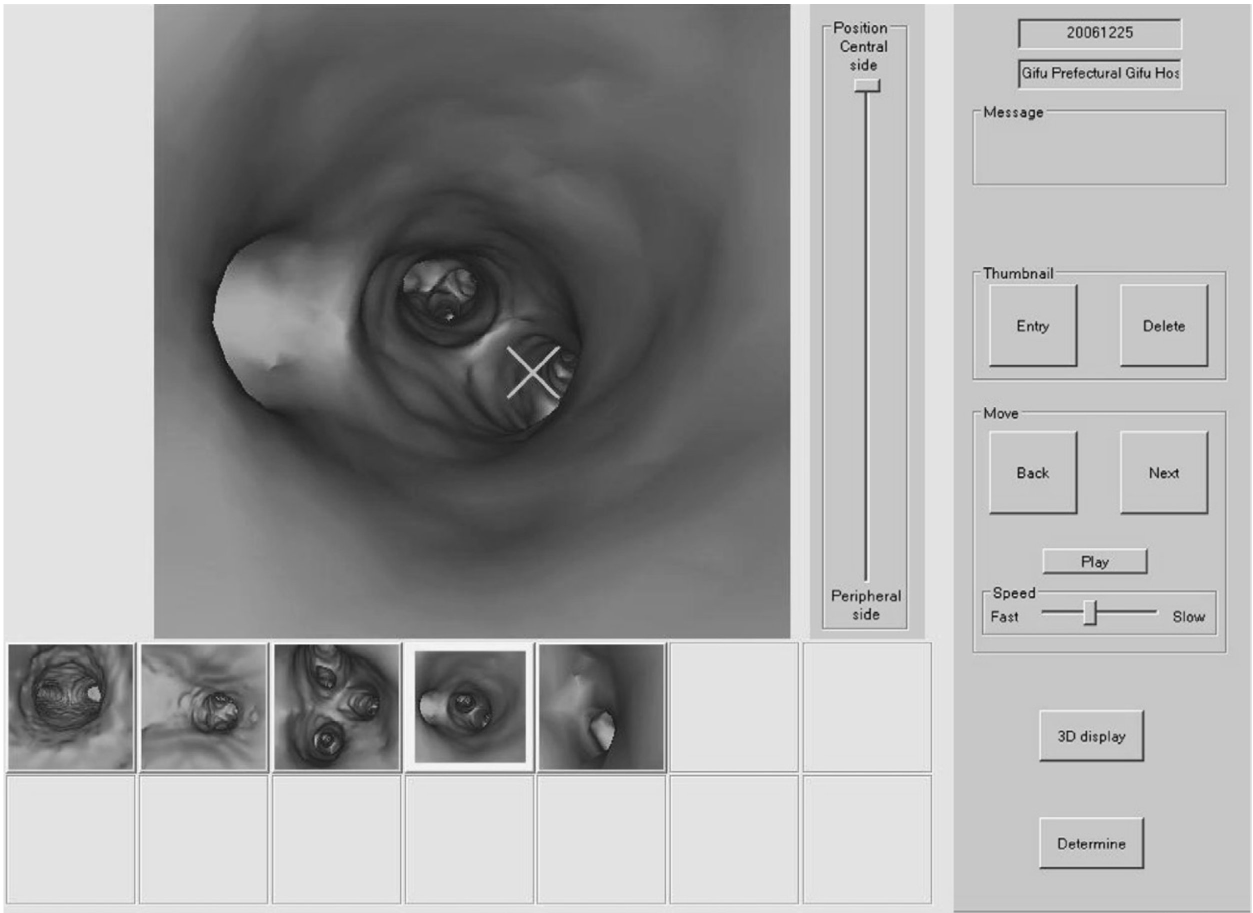

Fig. 4 Virtual image production, thumbnail registry. The cross on the virtual image shows the next target bronchus to which the bronchoscope should be advanced.

and diagnosis was impossible; however, based on operative findings and the clinical course, two of the three lesions were diagnosed as lung cancer (one adenocarcinoma and one lesion of unknown histological type), and the other as organized pneumonia. The median number of brush passes was one (0—1). Brush cytology was positive in 15 patients (46.9%), but there were no patients positive for only cytology.

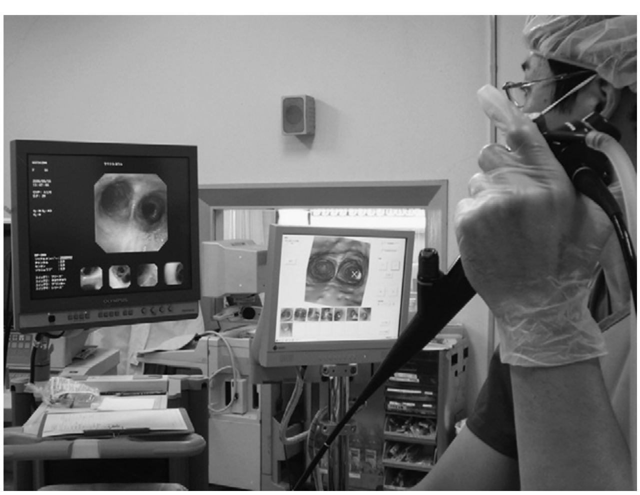

Fig. 5 Navigational bronchoscopy using the insertion guidance system. Using the system, virtual images (middle) of the target bronchus are displayed in comparison with real images (left). Based on these images, the bronchoscope is inserted to the target under direct vision.

The EBUS visualization yield and diagnostic yield according to the size and benign/malignant disease are shown in Table 1. In lesions $\leq$30 mm in size, the EBUS visualization yield was 91.7% (22/24), and the diagnostic yield was 79.2% (19/24). The median total examination time was 22.3 (9.8—41.5) min. No complications were observed.

4. Discussion

In recent years, due to multislice CT, high-resolution volume data have been readily obtained, allowing virtual bronchoscopy of peripheral areas. In addition, since CT data already obtained are used in virtual bronchoscopy, there is no additional cost or exposure of patients to radiation. In this study, CT data obtained at the time of the initial diagnosis were used, and no additional CT scanning was performed for virtual bronchoscopy. However, virtual images change according to the threshold. In the peripheral area, virtual image production depends on the experience of the physician and is time-consuming. To overcome these problems, we developed a system that can be readily used by physicians during bronchoscopic examination of peripheral

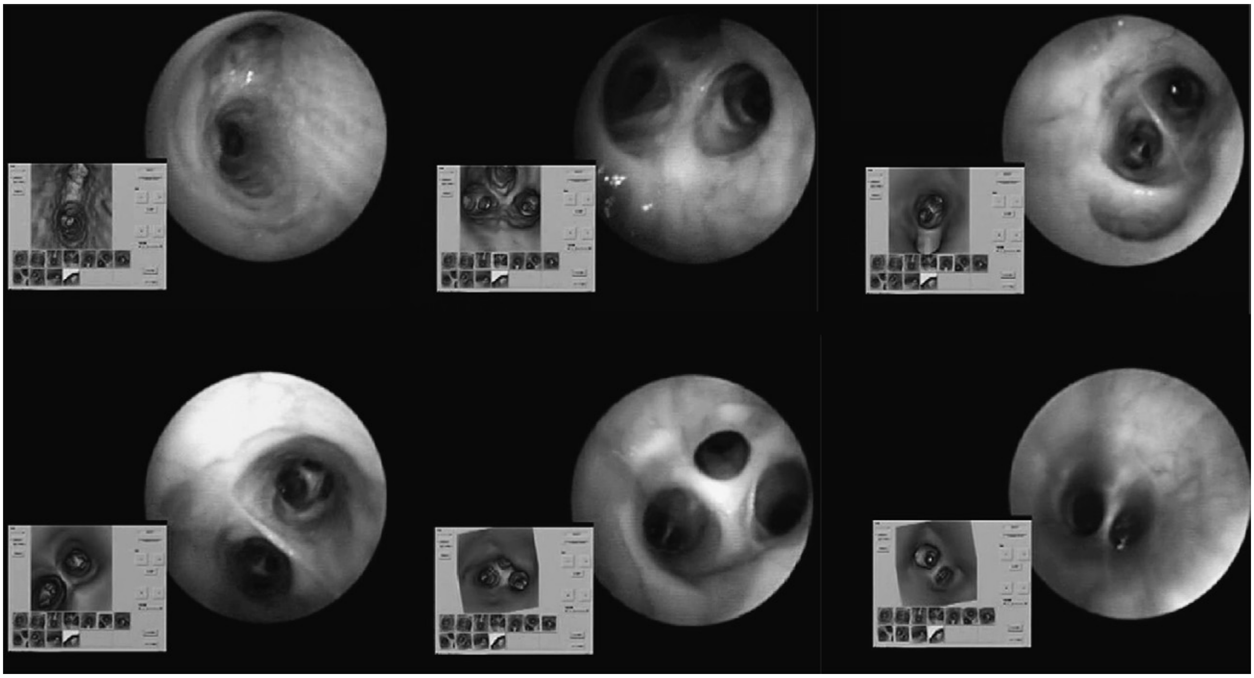

Fig. 6 Display of virtual images in comparison with real images. From the upper left to the upper right and from the lower left to the lower right, the bifurcation of the right upper lobe bronchus and the truncus intermedius to seventh-order bronchial branching are displayed. The two images of each pair became consistent by rotating the virtual image.

lesions. Using the present system, only the target is set, and no threshold setting is necessary. Accurate virtual image production in the observation range using a thin bronchoscope is possible. Since virtual images can be produced in a short time, physicians who perform bronchoscopy themselves can perform virtual bronchoscopy immediately before examination. In addition, since the produced virtual images can be effectively utilized by using the display in comparison with real images, the bronchoscope can be guided to the target in a short time. This system is therefore highly practicable.

VBN is useful for the navigation of a bronchoscope but does not allow the confirmation of its arrival at the lesion. Therefore, it is important to use other methods in combination with VBN. The EBUS system is relatively inexpensive, and its use in combination with a guide sheath further facilitates repeated sample collection from the lesion [17]. The advantage of VBN is its simplicity, which allows the insertion of a bronchoscope to the target under direct vision. In order to maximize the utilization of this advantage, a method allowing more peripheral insertion of a thinner bronchoscope is necessary. Therefore, we combined a bronchoscope insertion guidance system with a thin guide sheath-covered EBUS probe, and a thin bronchoscope with the minimum diameter.

With respect to studies on EBUS-GS, Kurimoto et al. [17] and Herth et al. [26] used a bronchoscope with an external diameter of 5.9—6.3 mm since they used an EBUS probe with an external diameter of 1.7 mm. Kikuchi et al. [18] used a thin EBUS probe similar to that used in the present study, while Asahina et al. [23] used a thin EBUS probe in combination with VBN, and both of these authors used not only a thin bronchoscope but also a thicker one. In addition, Asahina et al. did not use the system we employed in this study. In each study, the EBUS visualization yield varied (79.2—93.3%) among lesions but was 79.2% [18] or 80% [23] in lesions of ≤3 cm. In these studies, when lesions could not be visualized, the guide sheath was guided again using a curette under X-ray fluoroscopy. In the present study, without using a curette, the visualization yield in lesions of ≤3 cm (91.7%, 22/24) was comparable to or higher than the over-

Table 1 Diagnostic yield of EBUS-GS-guided TBB with the bronchoscope insertion guidance system

Size (mm)	Visible on EBUS	EBUS-GS pathologic diagnosis		
		Total	Malignant	Benign
≤20	13/15 (86.7)	11/15 (73.3)	9/12 (75)	2/3 (66.7)
20—30	9/9 (100)	8/9 (88.9)	7/8 (87.5)	1/1 (100)
>30	8/8 (100)	8/8 (100)	7/7 (100)	1/1 (100)
Total	30/32 (93.8)	27/32 (84.4)	23/27 (85.2)	4/5 (80)

Data are presented as number of lesions/total lesions (%).

all visualization yield in the above-mentioned studies. This may be because the guide sheath-covered EBUS probe could be inserted to the target bronchus in more peripheral areas under direct vision. As a result, the lesion could be visualized only by insertion of the probe in most cases.

The diagnostic yield in lesions ≤30 mm was 79.2% (19/24) in the present study. These lesions included 12 lesions that could not be visualized by fluoroscopy and whose diagnostic yield was 75%. These lesions are not indicated for conventional fluoroscopy-guided bronchoscopic biopsy. Taking this into consideration, the diagnostic yield provided by the present method may be higher than that of the conventional method. In addition, previous studies on EBUS-GS have shown diagnostic yields of 74% [17], 58.3% [18], and 63.3% [23] in lesions of ≤3 cm, and of 74% [17] and 70% [26] in lesions that could not be visualized by fluoroscopy. The diagnostic yield in the present study may be comparable to or higher than these yields. One reason for the higher diagnostic yield in the present study may be the above-described high lesion visualization yield by EBUS. It is also possible that there may be a reduction in navigation time due to the use of this system, allowing the collection of many samples if a longer time is used. Kikuchi et al. [18] and Asahina et al. [23] report mean numbers of collected samples of 3.5 and 2.8, respectively. In the present study, despite a short total examination time, a median of five samples could be collected. Asahina et al. reported a significantly lower number of tissue samples in cases that could not be compared to those that could be diagnosed. Although, we did not evaluate the cumulative diagnosis rate according to the number of tissue samples in this study, since the forceps used were of the same type, an increase in the number of samples may have contributed to the improvement of the diagnosis rate. On the other hand, the low diagnosis rate by brush cytology in this study may be due to a low number of brush passes and a small amount of collected cells because of the use of a small brush.

The high lesion visualization rate by EBUS and increase in the frequency of sample collection within the short examination time suggest the usefulness of the combination of the bronchoscope insertion guidance system, a thin bronchoscope, and EBUS-GS. To statistically clarify improvement in the diagnosis rate using this system and the shortening of the examination time, a multi-center randomized study is being conducted.

5. Conclusion

Using the proposed bronchoscope insertion guidance system, virtual image production and navigation of a bronchoscope to the target are readily performed. The method using this system in combination with a thin bronchoscope and thin EBUS-GS does not require large equipment or much time and is associated with a high diagnostic yield. This method is therefore highly promising as a routine method of biopsy for peripheral pulmonary lesions.

Conflict of interest statement

None declared.

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